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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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WRITTEN OPINION

(PCT Rule 66)

Applicant's or agent's file reference 3268.1003003.	Date of Mailing (*day/month/year*) 08 DEC 2004 REPLY DUE within 1 months/days from the above date of mailing

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US03/36975	19 November 2003 (19.11.2003)	20 November 2002 (20.11.2002)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C07K 5/00, 16/00; A61K 39/395; C12N 15/00 and US Cl.: 530/350, 387.3, 388.8; 424/134.1, 155.1; 435/69.7

Applicant

NORTH SHORE-LONG ISLAND JEWISH RESEARCH INSTITUTE

1. This written opinion is the first (first, etc,) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 20 March 2005 (20.03.2005).

Name and mailing address of the IPEA/US
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WRITTEN OPINION

International application No.
PCT/US03/36975

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-35, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 36-40, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-13, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the sequence listing part of the description:
pages 1-14, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☒ contained in the international application in printed form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE _____

☐ the claims, Nos. NONE _____

☐ the drawings, sheets/~~fig~~ NONE _____

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."*

WRITTEN OPINION

International Application No.
PCT/US03/36975

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	6-45.	YES
	Claims	1-5.	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-45.	NO
Industrial Applicability (IA)	Claims	1-45.	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

Claims 1-45 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:
The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

Claims 1-5 lack novelty under PCT Article 33(2) as being anticipated by Wen et al.

Claims 1-5 are drawn to a pharmaceutical composition comprising a polypeptide comprising a mammalian or human HMGB1 B box or functional variant thereof, in an amount sufficient to treat a disease or condition by increasing an immune response in an individual administered said pharmaceutical composition.

Wen et al teach the human HMG-1 polypeptide (see Figure 2), which inherently comprises an HMGB B box (e.g., amino acids 92-111 of Figure 2, which are identical to the HMGB B box (residues 1-20) of SEQ ID NO:5 (see page 11, line 25 of the specification)). The intended use as a pharmaceutical composition in an amount sufficient to treat a disease or condition by increasing an immune response in an individual is given no patentable weight.

Claims 1-45 lack an inventive step under PCT Article 33(3) as being obvious over Wen et al in view of Andersson et al and Krieg et al and Lode et al and Johnson D.A.

The claims are drawn to a pharmaceutical composition comprising a mammalian or human HMGB1 B box polypeptide, wherein said composition further comprises a vaccine, an adjuvant selected from an immunostimultory oligonucleotides (i.e., CpG sequences), an imidazoquinoline, Monophosphoryl lipid A and detoxified lipopolysaccharide; an antibody that binds a tumor-associated polypeptide, wherein the antibody is attached to said HMGB1 B box polypeptide; a method of stimulating or increasing an immune response in an individual in need of immunostimulation comprising administering said HMGB1 B box polypeptide; a method of treating cancer in an individual comprising administering said HMGB1 B box polypeptide.

Wen et al have been described supra. Wen et al do not teach administration of the HMGB1 B box polypeptide for stimulating an immune response or for treating cancer in an individual or pharmaceutical compositions comprising said HMGB1 B box polypeptide, further comprising a vaccine or the recited adjuvants or an antibody attached to said HMGB1 B box polypeptide. These deficiencies are made up for in the teachings of Andersson et al and Krieg et al and Lode et al and Johnson D. A.

Andersson et al teach that HMG-1 acts as a cytokine that specifically stimulates cytokine synthesis in human monocytes and HMG-1 can activate downstream cytokine cascades and participates in "cross-talk" for the propagation and amplification of downstream proinflammatory responses (see page 569). Andersson et al also teach that HMG-1 significantly increases cellular uptake of DNA, and bacterial DNA containing CpG motifs that activate monocyte cytokine synthesis are ubiquitous during infection (see page 569).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Krieg et al teach immunostimulatory nucleic acid molecules comprising unmethylated CpG sequences for treating, preventing or ameliorating a tumor or cancer, a viral, a fungal, a bacterial or parasitic infection in an individual and can be administered in conjunction with a vaccine (see columns 6 and 33). Krieg et al teach that unmethylated CpG containing nucleic acid molecules preferentially activate monocytic cells such as dendritic cells as well as NK cells (see column 13, lines 11-15) and induced spleen cells to secrete numerous cytokines including IL-3 and IL-12 (see column 33, lines 22-26). Krieg et al teach that for many pathogens, the humoral response contributes little to protection, and can even be detrimental" (see column 33, lines 56-61). Further, Krieg et al teach that unmethylated CpG nucleic acids induce Th1 type cytokines (IL-12 and IFN-gamma) and shift the immune response in a subject from a Th2 to a Th1 response.
Lode et al teach that targeting of cytokines into the tumor microenvironment using antibody-cytokine fusion proteins is highly effective in boosting cancer vaccines (see entire document).
Johnson D. A. teach pharmaceutical compositions and vaccine compositions that are effective to potentiate an immune response to one or more antigens, wherein the antigen is a tumor associated antigen (tumor specific antigen) (see columns 32-33). Johnson D. A. teach adjuvants for eliciting a predominantly Th-1 type response including monophosphoryl lipid A and CpG oligonucleotides.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a pharmaceutical composition comprising an HMGB1 B box polypeptide for inducing an immune response and for treating cancer in an individual and to attach the HMGB1 B box polypeptide to an antibody that binds a tumor-associated antigen for therapeutic benefit of cancer in view of Wen et al and Andersson et al and Krieg et al and Lode et al and Johnson D. A because Wen et al teach the human HMG-1 polypeptide, which inherently comprises an HMGB B box and Andersson et al teach that HMG-1 acts as a cytokine that specifically stimulates cytokine synthesis in human monocytes and HMG-1 significantly increases cellular uptake of DNA and Krieg et al teach DNA (immunostimulatory nucleic acids) comprising unmethylated CpG sequences for treating, preventing or ameliorating a tumor or cancer and can be administered in conjunction with a vaccine and Lode et al teach that targeting of cytokines into the tumor microenvironment using antibody-cytokine fusion proteins is highly effective in boosting cancer vaccines and Johnson teach pharmaceutical compositions and vaccine compositions comprising Th-1 type adjuvants (i.e., monophosphoryl lipid A and CpG oligonucleotides) that are effective in potentiating an immune response to one or more antigens, wherein the antigen is a tumor associated antigen. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared a pharmaceutical composition comprising the HMG-1 polypeptide taught by Wen et al and a CpG oligonucleotide for inducing an immune response in a patient and for treating cancer in a patient and it would have been obvious to one of ordinary skill in the art to have attached the HMG-1 polypeptide to an antibody for targeting the HMG-1 polypeptide (cytokine) into the tumor microenvironment, to more effectively boost a cancer vaccine as taught by Lode et al.

----------NEW CITATIONS----------

U.S. 6,207,646 B1 (KREIG et al) 27 March 2001 (27.03.2001), see entire document, especially columns 6, 11 and 33.